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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,800	03/31/2006	Christopher C. Broder	044508-5023	9160

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EXAMINER	
BLUMEL, BENJAMIN P	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,800	BRODER ET AL.	
	Examiner	Art Unit	
	BENJAMIN P. BLUMEL	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-19,23-26 and 31-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-19, 23-26 and 31-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants are informed that the rejections of the previous Office action not stated below have been withdrawn from consideration in view of the Applicant's arguments and/or amendments. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 16-19, 23-26 and 31-46 are examined on the merits.

Response to Amendment

The declaration filed on September 29, 2008 under 37 CFR 1.131 is sufficient to overcome the Bossart et al. (Virology, 2001) reference. The 35 U.S.C. 103(a) rejection has been overcome based on the statement that co-authors Wang and Eaton (Bossart et al.) did not contribute to the present invention and were under the direction of co-inventors Bossart and Broder. In addition, applicants have shown that the Virology reference was publicly available within 1 year of their earliest priority date and is considered to be not "by another". As a result of this declaration, the earliest priority date is November 15, 2001.

Claim Rejections - 35 USC § 112

(New Rejection) Claims 16-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the fusion of Nipah and Hendra viruses with cells *in vitro* with recombinant Nipah and Hendra virus Fusion proteins, does not reasonably provide enablement for inhibiting the fusion of any paramyxovirus with cells *in vitro* with the claimed fusion protein of SEQ ID NO:s 1 and/or 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature of the invention/Breadth of the claims. The claims are drawn to a method of inhibiting the fusion between the membrane of a paramyxovirus or a virus of the *Paramyxovirinae* subfamily and the plasma membrane of a cell by administering an effective amount of SEQ ID NO: 1 (Hendra virus Fusion (F) protein) and/or SEQ ID NO: 2 (Nipah virus Fusion protein) with a pharmaceutically acceptable carrier.

State of the prior art/Predictability of the art. The art recognizes that Hendra and Nipah viruses, while be classified in the *Paramyxoviridae* family of viruses, limited homology is found with the other viruses of this family. For example, Harcourt et al. (Virology, 2000) teach significant amino acid differences of the fusion protein from Nipah and Hendra viruses when compared to other viruses from various paramyxovirus genuses (see table 4). In particular, the 20 residue amino terminal end reveals limited similarities. Furthermore, the inventors co-authored a paper published in Journal of Virology in 2002 which teaches that Hendra and Nipah viruses possess a larger species tropism with regard to cell fusion and infection as compared to other paramyxoviruses. This different tropism exposes how Hendra and Nipah viruses may target different receptors compared to paramyxoviruses. In addition, applicants have argued that based on Wang et al., one skilled in the art would not expect the fusion protein from Hendra and/or Nipah viruses to inhibit any paramyxovirus to fuse with target cells given the numerous differences between HeV or NiV and the other viruses from the subfamily *Paramyxovirinae* (see page 7 of response). Therefore, in view of the teaches above, the ability a F protein from Hendra or Nipah virus to inhibit the fusion/infection of any paramyxovirus is not enabled since the protein involved lacks homology across species, while cellular tropism is distinct and the viruses

of the *Paramyxoviridae* family when comparing HeV and NiV with non-henipavirus species also reveals significant divergence.

Working examples. No working example is disclosed in the specification.

Amount of experimentation necessary. Additional research is required in order to determine how effective a viral F protein from Hendra or Nipah would be at inhibiting the infection of a target cell by any paramyxovirus.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

(Prior Rejection Maintained) Claim 39 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition based on Nipah or Hendra Fusion proteins, does not reasonably provide enablement for a vaccine for Nipah or Hendra based on such a protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 39 recites, "the composition is formulated as a vaccine", however as stated in the previous Office action (page 6), such a vaccine based on Hendra and/or Nipah virus Fusion proteins is not recognized in the art of Paramyxovirus research and the specification does not contain any working examples to showing such a subunit vaccine based on the fusion proteins of SEQ ID NO:s 1 and/or 2. Therefore, the rejection is maintained for reasons of record.

Claim Rejections - 35 USC § 103

(New Rejection Necessitated by Amendments) Claims 16, 18, 19, 23-26, 31-38, 40-43, 45 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Compans and Ranjit (US Pat. 5,843,451), Lambert et al. (PNAS, 1996), Young et al. (Virology, 1997), Williamson et al. (Journal of Comparative Pathology, 1999) and Harcourt et al. (Virology, 2000).

The claimed invention is drawn to a method of inducing an immune response to a virus by administering a polypeptide comprising or consisting of SEQ ID NO: 1 and/or SEQ ID NO: 2. The virus can either be a paramyxovirus, a virus of the subfamily *Paramyxovirinae*, or one of the viruses of Hendra or Nipah. The polypeptide(s) can be administered in a pharmaceutically acceptable carrier via oral, subcutaneous, intravenous, intramuscular, or intraperitoneal routes. The subject used can be a human. The method also requires that the polypeptides administered inhibit the fusion of a virus from the *Henipavirus* genus with that of a target cell's plasma membrane.

Compans and Ranjit teach the development of a subunit immunogenic composition based on paramyxovirus F protein that can be administered with an acceptable pharmaceutical carrier. Compans and Ranjit teach that intranasal, intravenous and other routes can be used in administering such compositions. However, Compans and Ranjit do not teach the administration of SEQ ID NO:s 1 and/or 2 in order to induce an immune response, nor do they teach Hendra or Nipah viruses. *See columns 1, 3 and 6.*

Lambert et al. teach the use of fragments from the fusion proteins of paramyxoviruses, respiratory syncytial virus (RSV), human parainfluenza virus 3 (HPIV-3) and measles virus (MV) in order to inhibit viral fusion of target cells. Through their research, Lambert et al.

determine that these fragments are potent antiviral proteins which can be tested for clinical applications. However, Lambert et al. do not teach the use of SEQ ID NO: 1 and/or SEQ ID NO: 2 or the inhibition of cell fusion by a virus from the *Henipavirus* genus.

Young et al. teach the analysis of peptide based inhibitors of Newcastle Disease virus (NDV, which is a paramyxovirus) fusion with a target cell. Young et al. employ a fragment of the NDV fusion protein of the amino acids-ALDKLEESNSKLDKVNVKLT, which are residues 478-497, in order to inhibit fusion. However, Young et al. do not teach the use of SEQ ID NO: 1 and/or SEQ ID NO: 2; or the inhibition of cell fusion by a virus from the *Henipavirus* genus.

Williamson et al. teach the administration of Hendra viruses to guinea-pigs and fruit bats (a carrier of Hendra virus) in order to determine if the virus can be transmitted through the placenta. Some of the fruit bats reported Hendra elicited antibody titers of up to 160. *See pages 201 and 206.*

Harcourt et al. teach the Hendra and Nipah F proteins that contain the polypeptides of SEQ ID NO:s 1 and 2 from residues 447-487 (see figure 5). Harcourt et al. also teach the importance of these viruses to humans since outbreaks in 1999 killed approximately 40% of those infected in Malaysia and Singapore.

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Compans and Ranjit, Lambert et al. and Young et al. in order to inhibit viral fusion and infection of a virus from the *Henipavirus* genus and to also induce an immune response against the polypeptides of SEQ ID NO:s 1 and/or 2. One would have been motivated to do so, given the suggestion by Compans and Ranjit, Lambert et al. and Young et al. that the method be used to induce immune responses to paramyxovirus F proteins by administering an immunogenic

composition based on the F protein of paramyxoviruses; the method also be used to inhibit the fusion of non-Henipavirus paramyxoviruses with cells by administering the F protein; and also by administering a 20 amino acid segment of a NDV F protein in order to inhibit viral fusion with a target cell, respectively. There would have been a reasonable expectation of success, given the knowledge that the experimental administration of Hendra viruses to guinea-pigs and fruit bats resulted in humoral responses, as taught by Williamson et al., and also given the knowledge that the complete amino acid sequence for the Hendra and Nipah F protein (which contains SEQ ID NO:s 1 and 2) was known prior to the instant invention, as taught by Harcourt et al. Furthermore, even though the combined references do not specifically teach using the specific residues of SEQ ID NO:s 1 and 2, since the complete F protein sequence is presented by Harcourt et al., and Young et al. use a fragment similar in size to the claimed sequences, one of ordinary skill in the art would know how to make fragments (which would include the fragments presented by SEQ ID NO:s 1 and 2) from the published sequence of Harcourt et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments:

Applicants argue that Lambert et al. does not teach the use of peptides derived from Hendra or Nipah virus F proteins to inhibit cell fusion or induce an immune response.

In response, it is acknowledged that Lambert et al. do not teach these limitations, however, they do establish the basis for testing F proteins of other paramyxoviruses for their inhibition of viral fusion/infection of target cells.

Applicants also argue that since Wang et al. teach significant amino acid differences between the well established species of paramyxoviruses compared to that of Nipah and Hendra viruses, one skilled in the art would not be expected to have success at using the teachings of Lambert et al. and Young et al. at inhibiting Hendra or Nipah virus fusion/infection with SEQ ID NO:s 1 and 2, respectively.

In response, while it is acknowledged that given the teachings of Wang et al., one skilled in the art would not expect to inhibit any paramyxovirus (such as RSV) fusion with a target cell by administering a fragment of the F protein from Hendra or Nipah virus (see the 35 U.S.C. 112 1st paragraph rejection above). However, since Lambert et al. and Young et al. provide the basis for testing F proteins of paramyxoviruses for potential inhibitory properties of viral fusion, one skilled in the art would be capable of testing fragments of the F protein of Nipah or Hendra viruses for their inhibitory effects since this would only require the substitution of a known sequence in the methods proposed by Lambert et al. and Young et al. Furthermore, with regard to inducing an immune response reactive to any paramyxovirus by administering SEQ ID NO:s 1 and/or 2, the homology reported by Harcourt et al. in Table 4 indicates that as the F proteins are processed by antigen presenting cells, some of the resulting epitopes presented would elicit an immune response that would be specific for paramyxoviruses in addition to Nipah and Hendra viruses.

(New Rejection Necessitated by Amendments) Claims 23-26, 31-38 and 40-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Compans and Ranjit (*supra*), Young et al. (*supra*), Williamson et al. (*supra*), Harcourt et al. (*supra*) and Bembridge et al. (Journal of General Virology, 2000).

The claimed invention is drawn to a method of inducing an immune response to a virus by administering a fusion polypeptide comprising or consisting of SEQ ID NO: 1 and/or SEQ ID NO: 2. The virus can either be a paramyxovirus, a virus of the subfamily *Paramyxovirinae*, or one of the viruses of Hendra or Nipah. The polypeptide(s) can be administered in a pharmaceutically acceptable carrier via oral, subcutaneous, intravenous, intramuscular, or intraperitoneal routes. The subject used can be a human.

The teachings of Compans and Ranjit are discussed above, however, they do not teach the administration of fusion proteins containing SEQ ID NO:s 1 and/or 2 in order to induce an immune response, nor do they teach Hendra or Nipah viruses.

The teachings of Young et al. are discussed above, however, they do not teach the administration of fusion proteins containing SEQ ID NO:s 1 and/or 2 in order to induce an immune response, nor do they teach Hendra or Nipah viruses.

The teachings of Williamson et al. are discussed above, however, they do not teach the administration of fusion proteins that contain SEQ ID NO:s 1 and/or 2 to induce an immune response.

The teachings of Harcourt et al. are discussed above, however, they do not teach the administration of fusion proteins containing SEQ ID NO:s 1 and/or 2 to induce an immune response.

Bembridge et al. teach the administration of plasmids encoding the G and F proteins of the paramyxovirus RSV to mice with and without plasmids encoding certain cytokines. Bembridge et al. employ certain cytokines genes in order to determine if their presence would direct the T cell response to a Th2 response. Bembridge et al. also suggest that plasmids

encoding a fusion protein based on RSV F proteins and Th2 associated cytokines since the presence of these proteins being administered simultaneously generated better results *in vivo*. *See pages 2519 and 2522.*

It would have been obvious to one of ordinary skill in the art to modify the methods taught by Compans and Ranjit and Young et al. in order to inhibit viral fusion and infection of a virus from the *Henipavirus* genus and to also induce an immune response against the polypeptides of SEQ ID NO:s 1 and/or 2. One would have been motivated to do so, given the suggestion by Compans and Ranjit and Young et al. that the method be used to induce immune responses to paramyxovirus F proteins by administering an immunogenic composition based on the F protein of paramyxoviruses; and also by administering a 20 amino acid segment of a NDV F protein in order to inhibit viral fusion with a target cell, respectively. There would have been a reasonable expectation of success, given the knowledge that the experimental administration of Hendra viruses to guinea-pigs and fruit bats resulted in humoral responses, as taught by Williamson et al., also given the knowledge that the complete amino acid sequence for the Hendra and Nipah F protein (which contains SEQ ID NO:s 1 and 2) was known prior to the instant invention, as taught by Harcourt et al., and also given the knowledge that generating a fusion protein with RSV F proteins and cytokines (i.e., IL-4) of interest may improve antibody responses as the cytokine directs Th2 based immune responses, as taught by Bembridge et al. Furthermore, even though the combined references do not specifically teach using the specific residues of SEQ ID NO:s 1 and 2, since the complete F protein sequence is presented by Harcourt et al. and Young et al. use a fragment similar in size to the claimed sequences, one skilled in the art would known how to make fragments (which would include the fragments

presented by SEQ ID NO:s 1 and 2) from the published sequence of Harcourt et al. Thus the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim Objections

Claim 31 is objected to because of the following informalities: the claim recites, "…response to by a paramyxovirus…", however, it appears that "by" is out of place. Appropriate correction is required.

Applicant is advised that should claims 17, 25 and 40 be found allowable, claims 19, 26 and 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof since the only species of viruses in the *Henipavirus* genus are that of Hendra and Nipah viruses. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Summary

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BENJAMIN P. BLUMEL whose telephone number is (571)272-4960. The examiner can normally be reached on M-F, 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stacy B Chen/
Primary Examiner, Art Unit 1648

/BENJAMIN P BLUMEL/
Examiner
Art Unit 1648